

Ontology Nanomaterials safety

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Knowledge development – difference in philosophy

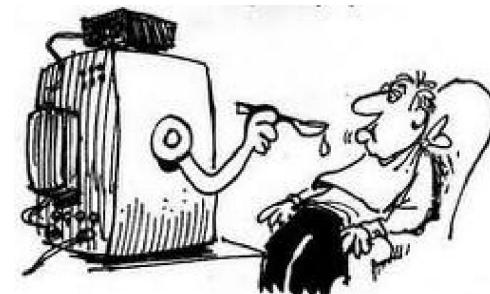
Human readable format

- Provide database
- End-user builds knowledge.



Machine readable format

- Provide expert system
- End-user is presented with an answer.



- In reality, perhaps both?

VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
AGOYDEPCAN(C)[C@H]3C[C@@H](C)O[C@@H](O[C@@H]2C
(C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

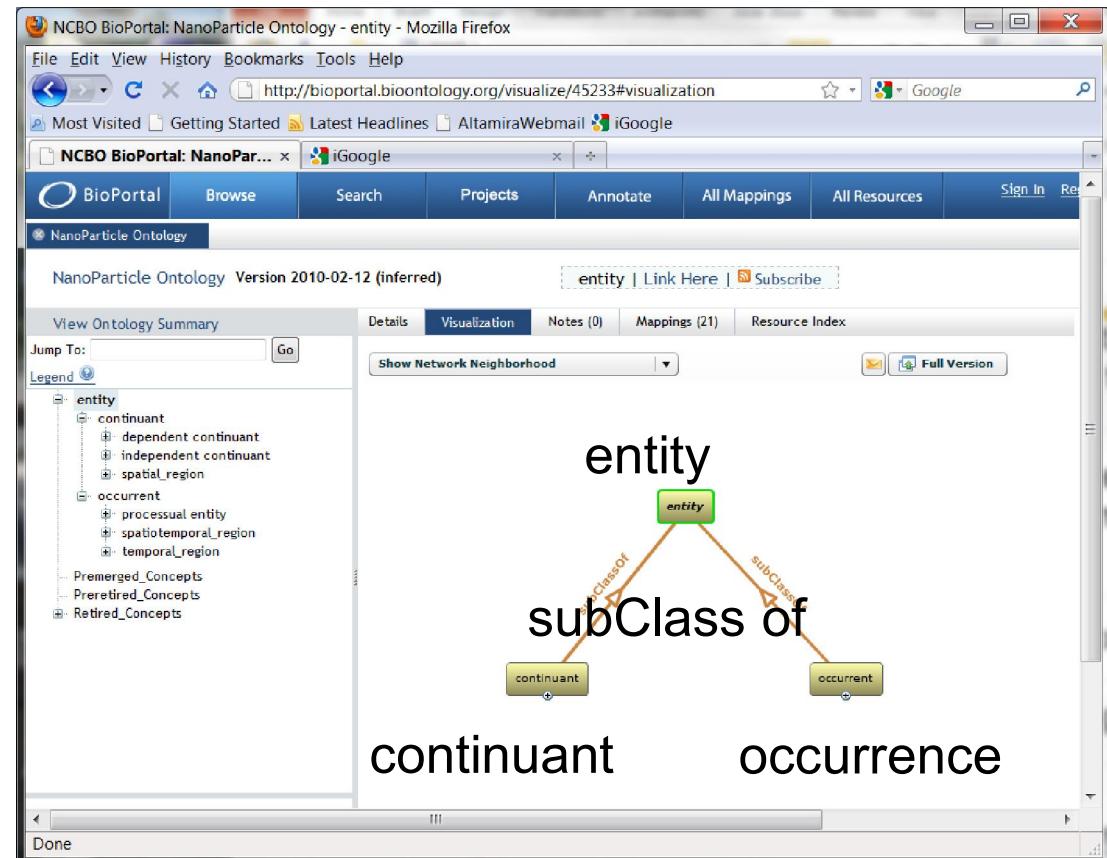
Ontology

- A formal representation of a set of concepts and their relationships, linking facts to related terms in a ***causal*** order
- To formulate domain knowledge and integrate knowledge from diverse domains
 - Gene ontology
 - <http://www.geneontology.org/>
 - ChEBI (chemical entities of biological interest)
 - <http://www.ebi.ac.uk/chebi/>
 - NPO for Cancer Nanotechnology Research
 - <http://www.nano-ontology.org/>
 - Toxicology ontology

A quick look at NanoParticle Ontology (NPO)

...to represent the knowledge underlying the description, preparation, and characterization of nanomaterials in cancer nanotechnology research in NCI...

J Biomed Inform, in press.
doi:[10.1016/j.jbi.2010.03.001](https://doi.org/10.1016/j.jbi.2010.03.001).



<http://bioportal.bioontology.org/visualize/45233/>

VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3 AGOYDEPGAOX

Example: Ontologies can be useful

The image displays two screenshots of biological databases. On the left is the AmiGO interface, which features a search bar and a sidebar for navigating the Gene Ontology database. The sidebar shows a tree structure for the cellular component category, including terms like molecular function, biological process, and cellular component. A blue arrow points from this sidebar towards the left side of the slide, labeled "Gene ontology". On the right is the ChEBI interface, showing a search bar and a sidebar for navigating the chemical ontology database. The sidebar shows a tree structure for the molecular entity category, including terms like role, biological role, application, chemical role, and molecular structure. A green arrow points from this sidebar towards the right side of the slide, labeled "Chemical ontology".

the Gene Ontology AmiGO

Search the Gene Ontology database

(GO terms) (genes or proteins) (exact match)

Submit Query

molecular_function
biological_process
cellular component

- + extracellular region
- + cell
- + virion
- + membrane-enclosed lumen
- + macromolecular complex
- + organelle
- + extracellular region part
- + organelle part
- + virion part
- + synapse part
- + cell part
- + synapse
- + symplast

GO database release 2010-05-01
Cite this data • Terms of use • GO helpdesk
Copyright © 1999-2009 the Gene Ontology.

role
+ biological role
+ application
+ chemical role
molecular structure
+ **molecular entity**

- + inorganic molecular entity
- + ion
- + radical
- + homoatomic molecular entity
- + transition element molecular entity
- + main group molecular entity
- + s-block molecular entity
- + d-block molecular entity
- + polyatomic entity
- + exotic molecular entity
- + group
- + atom

Entity of the month
5 May 2010, Mephedrone

ChEBI

Enter Text Here

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News RSS 05 May 2010 - ChEBI Release 68 ChEBI release 68 is now available, with 549,319 total entities, of which 21,075 are fully annotated to the star level.

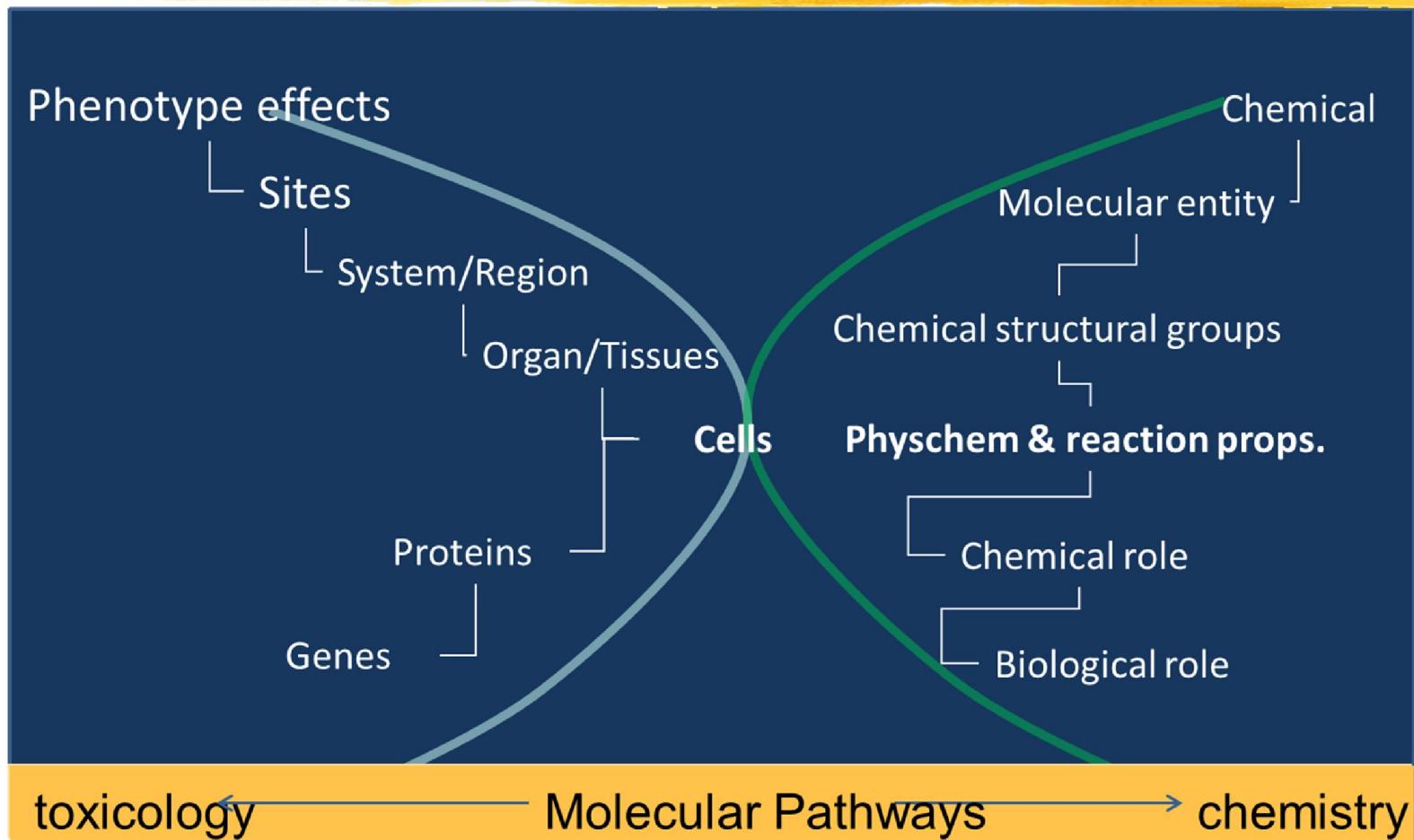
Search Search for ★★★ only

Entity of the month 5 May 2010, Mephedrone

CN(C)c1ccc(cc1)C(=O)C(C)C

VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
AGOYCEI-C1=CC=C(C=C1C(=O)C(C(=O)O)=NN2CC)OCO3
(C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]1

Conceptual framework of chem-tox ontology



Example: the power of ontology

from biological perspective

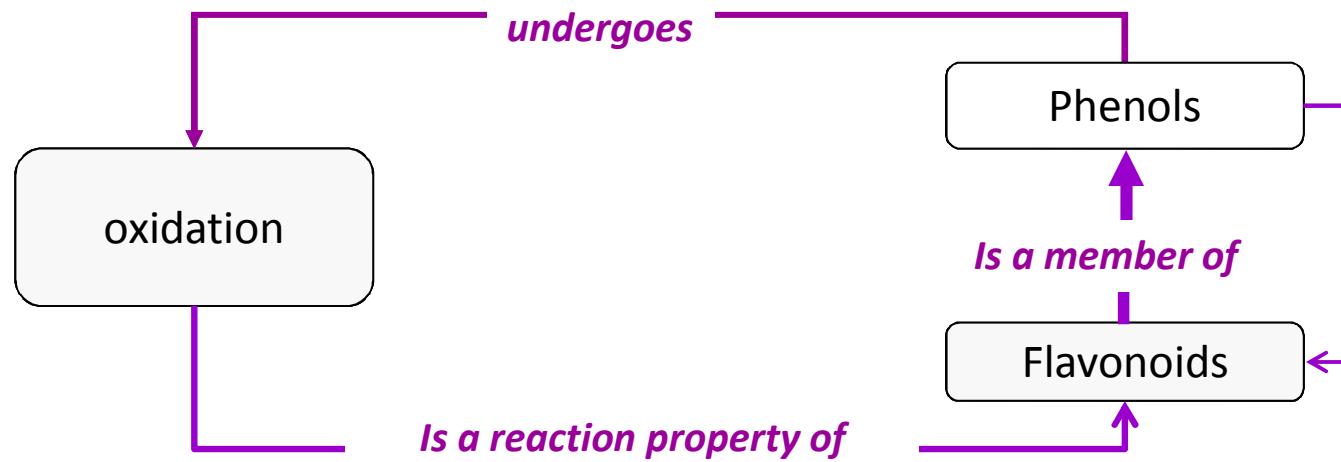
- Mutations and cancer endpoints are affected by genes in cell cycle and cell cycle checkpoint



<http://www.geneontology.org/GO.ontology.relations.shtml>

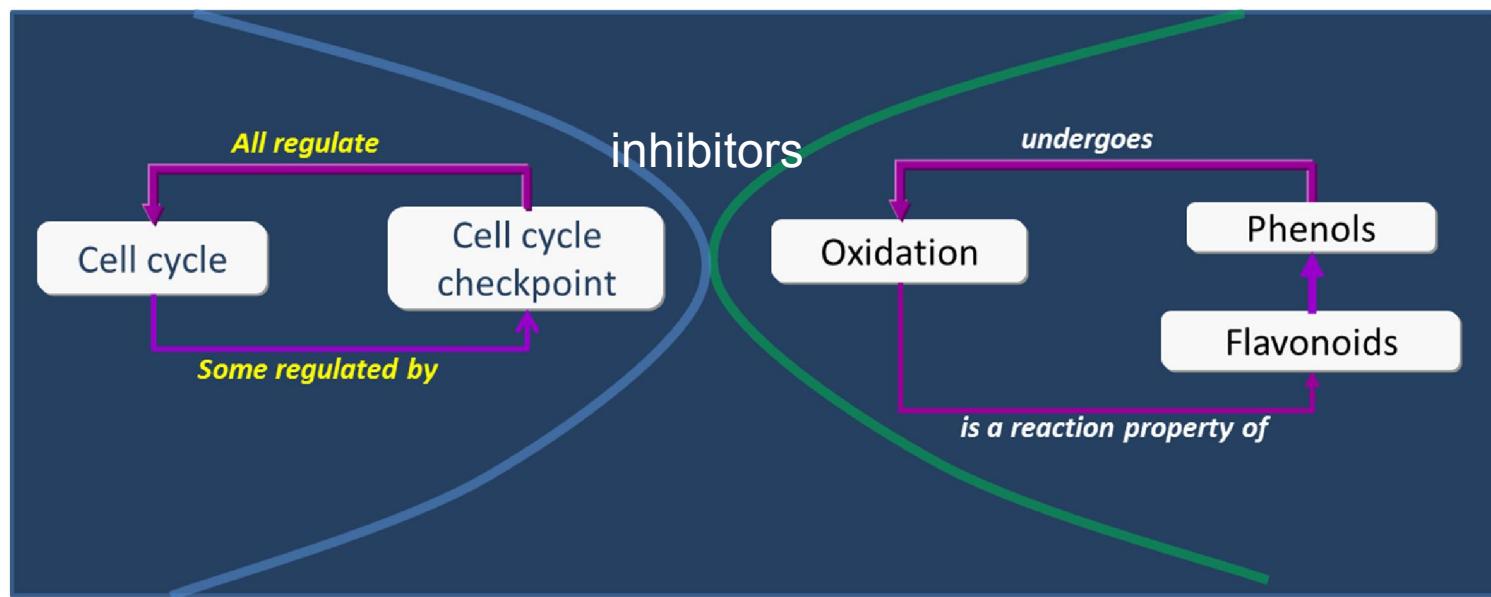
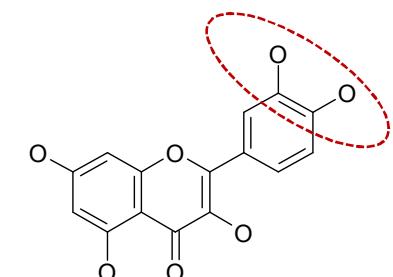
Example: the power of ontology from chemical perspective

- Flavonoids is an important chemical class in foods and drugs
 - phenol undergoes oxidation reaction
 - Role: often used as an antioxidant



Mechanistic reasoning by gene and chemical ontologies

- Flavonoid class is highly associated with gene expression of CDC25A, CDK, etc. (NCI/DTP data mining)
- Flavonoids are small molecule inhibitors
 - Requires hydrogen bonding in the pocket.
 - Oxidation of phenols adversely affects.



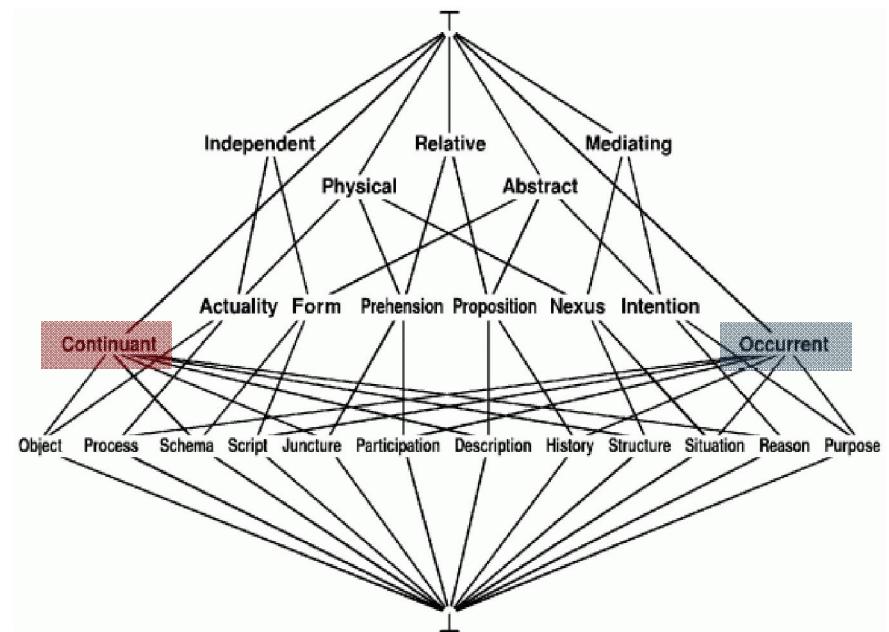
Knowledge Representation Ontology

- independent
- dependent (relative)
- mediating

- physical (object)
- abstract (description)

- continuant – thing/object
- occurrent – process
- thematic role – role

The Lattice



John F. Sowa *Knowledge Representation: Logical, Philosophical, and Computational Foundations*, Brooks Cole Publishing Co., CA 1999.

Nanoparticles safety ontology

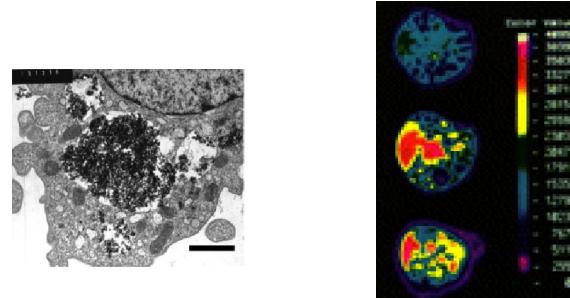
- Framework
 - subatomic particles → atoms → molecules → nanoparticles → mesoporous particles →
- To model ENM interactions at the biological interface
 - Nano materials identification and characterization
 - Biological interface characterization
- To represent *in vitro* toxicity data and link to *in vivo* data

Knowledge discovery - food intake

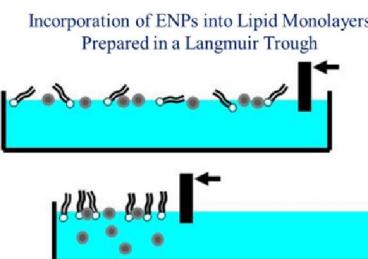
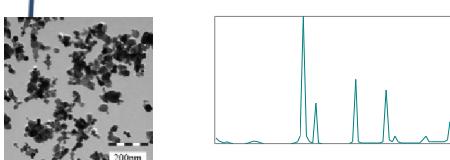
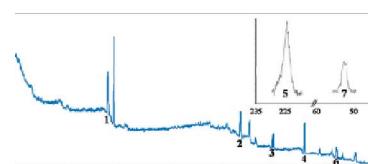
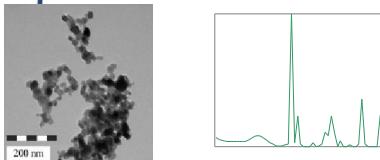
synthesis

Microwave-Based Quantum Dot Synthesis

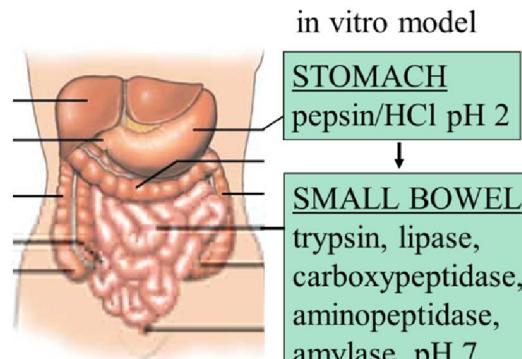
biological characterization



identification/characterization



biological process

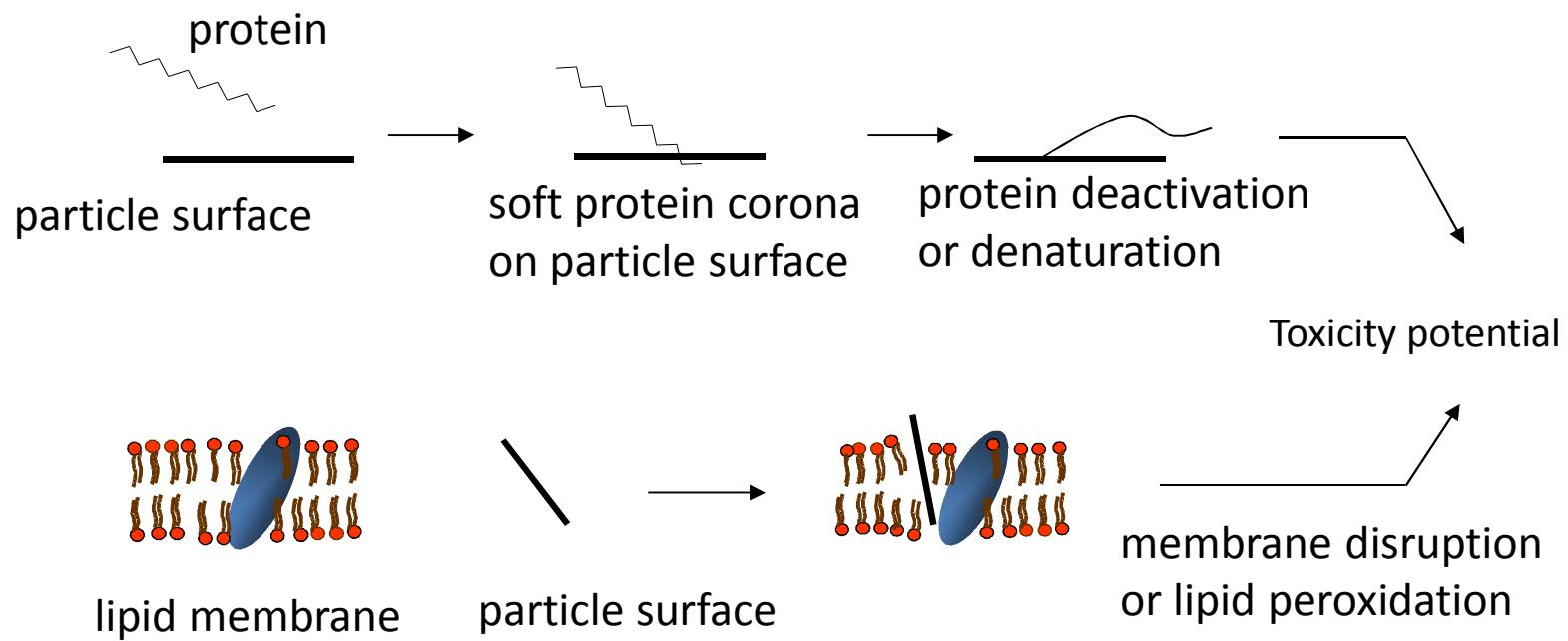


Alt LLC

VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
AGOYDERGAOXOC1-LFRDGGE-SANCN(C)[C@H]2C[C@@H](C)C[C@H]2C[C@H]2C
(C)[C@H](O)C[C@H]1C[C@H]2C[C@H](O)C[C@H]1C[C@H]2C[C@H]2C
(C)[C@H](O)C[C@H]1C[C@H]2C[C@H](O)C[C@H]1C[C@H]2C[C@H]2C

Knowledge discovery – biological interface

- To model simple/plausible modes of ENM interactions with biological systems involved in safety

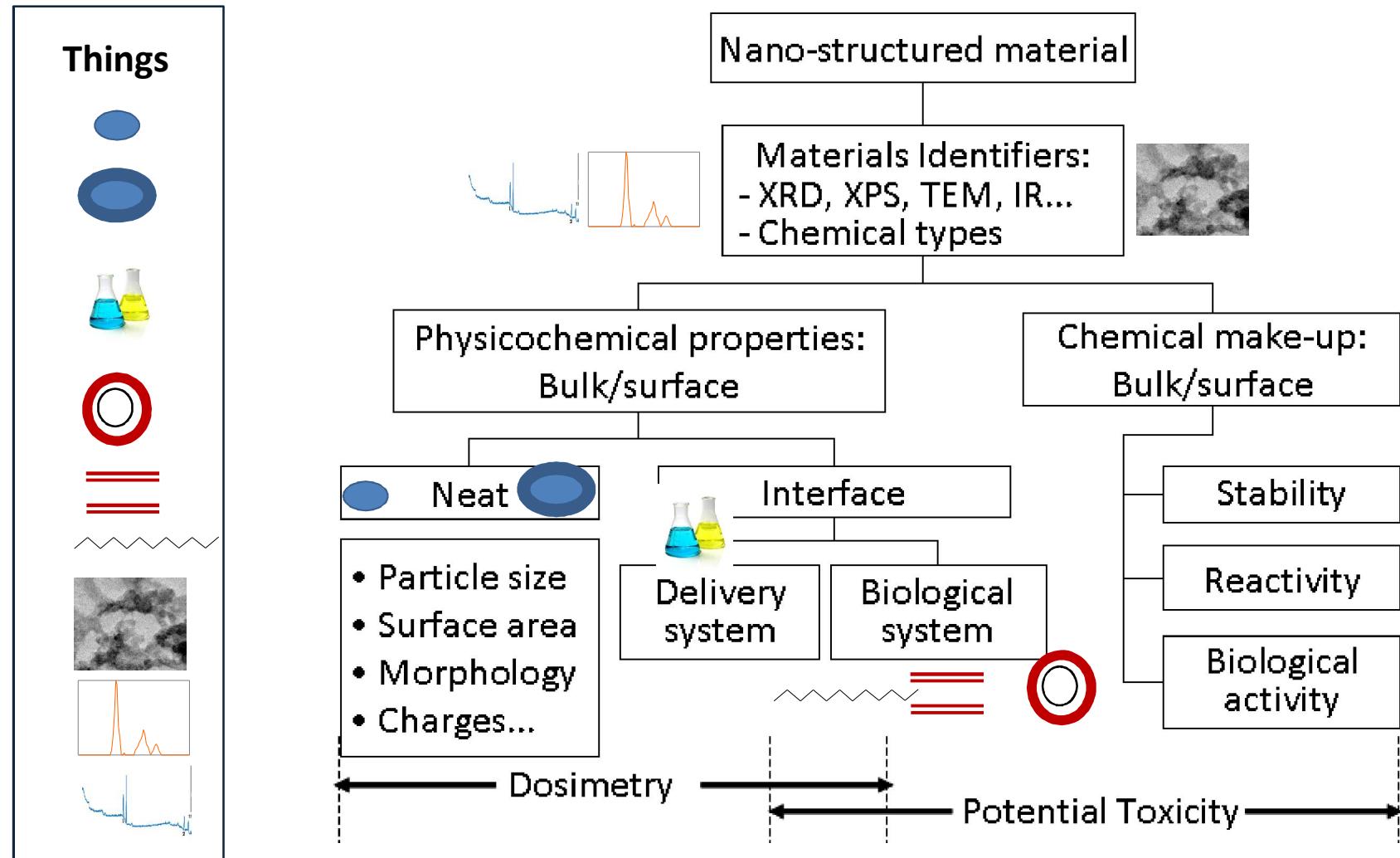


VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3 AGOYDEPGAC(O[C@H]1[C@@H](O)[C@@H](O)[C@H](O)[C@H](O)[C@H](C)C(=O)O[C@H]2C (C)[C@H](O[C@H]1C[C@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]1

Representing things and happenings...

physical thing - object	abstract things - property	happening - process
particle core		
particle surface		
medium		
cells		
proteins		
lipid membrane		
	chemical make-up charge size spectra/microscopy	adsorbs binds catalyzes decomposes reacts

Identification/Characterization of Nanomaterials

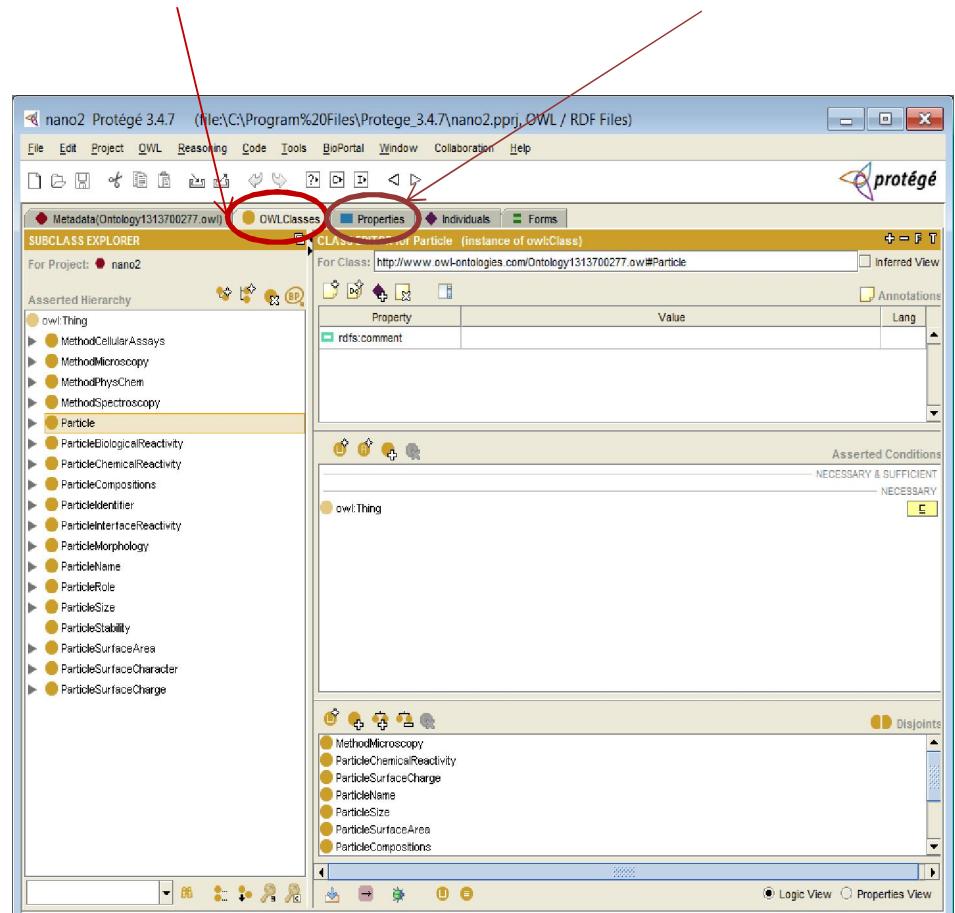


VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3 AGOYDHFQKREOTFSAN[O@C@H]C[C@H](O)[C@@H](C)O1[C@@H](C)C(=O)O[C@H]1

Classes in nano (particles or ENMs) ontology

- Particle
- ParticleAtInterface
- ParticleBiologicalReactivity
- ParticleChemicalReactivity
- ParticleCompositions
- ParticleIdentifier
- ParticleName
- ParticleMorphology
- ParticleRole
- ParticleSize
- ParticleSurfaceArea
- ParticleSurfaceCharge
- ParticleSurfaceTreatment
- ParticleStability
- MethodCellularAssay
- MethodPhysChem
- MethodSpectroscopy
- MethodMicroscopy

THING (CLASS) PROPERTIES



VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
 AGOYDEPGAOXOCKCGTDFFPDKC4DCH1DQD7VJF5@H]O[C@@H]2C
 (C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

Simple example: classification

TiO₂
 size 21 nm
 XRD spectrum
 TEM image

TiO₂ (particle)

TEM image
 (Identifier)

XRD spectrum
 (Identifier)

avg. 21 nm (size)

CLASS Hierarchy

PROPERTY BROWSER

PROPERTIES

SUBCLASS EXPLORER

For Project: nano2

Asserted Hierarchy

- ▶ **Particle**
- ▶ **ParticleAtInterface**
- ▶ **ParticleBiologicalReactivity**
- ▶ **ParticleChemicalReactivity**
- ▶ **ParticleCompositions**
- ▶ **ParticleIdentifier**
 - ▶ **BatchNumber**
 - ▶ **CatalogID**
 - ▶ **Impurity**
 - ▶ **LotNumber**
 - ▶ **Manufacturer**
 - ▶ **ManufacturingProcess**
 - ▶ **ParticleImage**
 - ▶ **ParticleSpectrum**
 - ▶ **ParticleType**
 - ▶ **Provider**
 - ▶ **Source**
 - ▶ **SynthesisLaboratory**
 - ▶ **SynthesisMethod**
- ▶ **ParticleMorphology**
- ▶ **ParticleName**
- ▶ **ParticleRole**
- ▶ **ParticleSize**
- ▶ **ParticleStability**
- ▶ **ParticleSurfaceArea**

PROPERTY BROWSER

For Project: nano2

Object **Data type** **Annotation**

Object properties

- ▶ **hasBiologicalReactivity ↔ isBiologicalReactivity**
- ▶ **hasChemicalReactivity ↔ isChemicalReactivity**
- ▶ **hasImages ↔ isImageOf**
- ▶ **hasImpurity ↔ isImpurityOf**
- ▶ **hasInterfacialReactivity ↔ isInterfacialReactivity**
- ▶ **hasManufacturer ↔ isManufacturerOf**
- ▶ **hasMembers ↔ isMemberOf**
- ▶ **hasMorphology ↔ isMorphologyOf**
- ▶ **hasName**
- ▶ **hasRole ↔ isRoleOf**
- ▶ **hasSize**
- ▶ **hasSpectrum**
- ▶ **hasSurfaceArea**
- ▶ **hasSurfaceCharge**
- ▶ **hasSurfaceTreatment**
- ▶ **isBiologicalReactivity ↔ hasBiologicalReactivity**
- ▶ **isChemicalReactivity ↔ hasChemicalReactivity**
- ▶ **isImageOf ↔ hasImages**
- ▶ **isImpurityOf ↔ hasImpurity**
- ▶ **isInterfacialReactivity ↔ hasInterfacialReactivity**
- ▶ **isManufacturerOf ↔ hasManufacturer**
- ▶ **isMemberOf ↔ hasMembers**
- ▶ **isMethodFor**

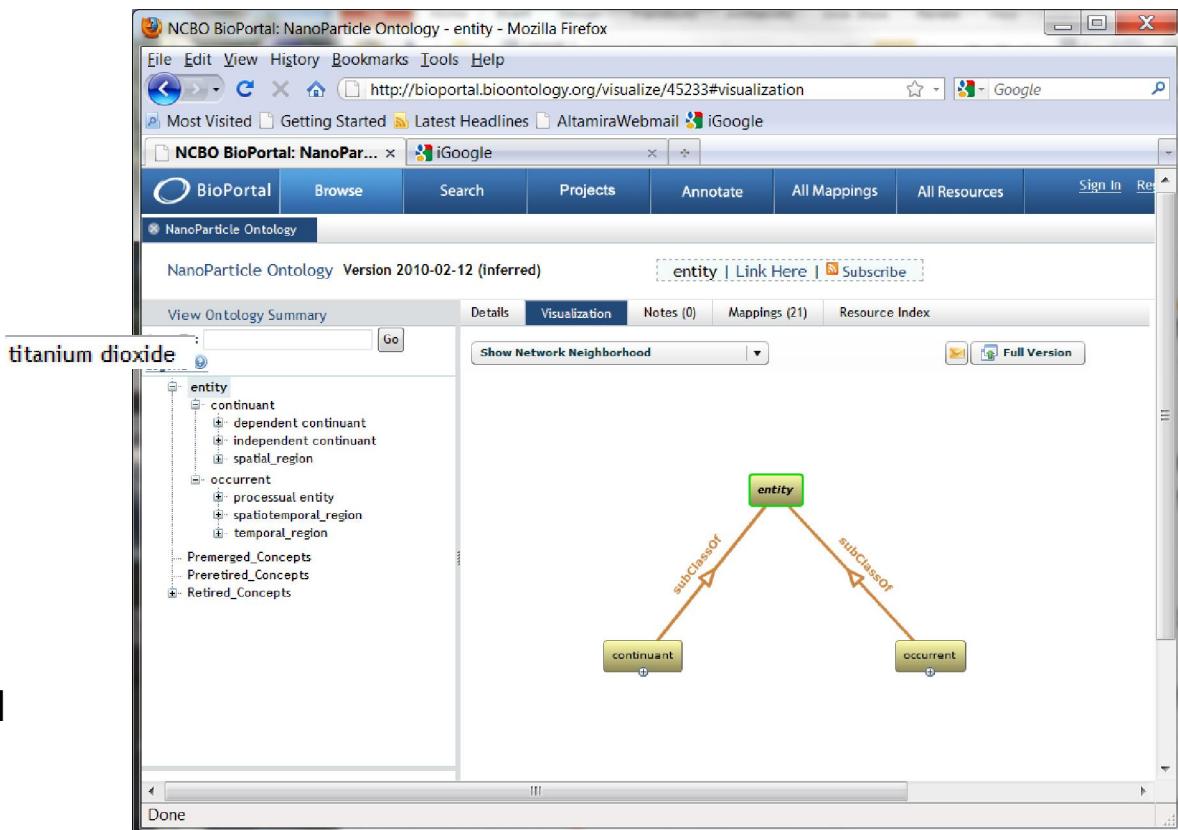
Super Properties

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AGOYDEP@H]3C[C@@H](C)O[C@@H](O[C@@H]2C
(C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

TiO₂

avg. 21 nm
XRD spectrum
TEM image

- + Entity
 - + object
 - + dependent
 - + independent
 - + spatial region
 - + process
 - + process entity
 - + spatio-temporal
 - + temporal



VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
AGOYDEP[CA]C[C@H]3C[C@@H](C)O[C@@H](O[C@@H]2C
(C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

Back to NPO example

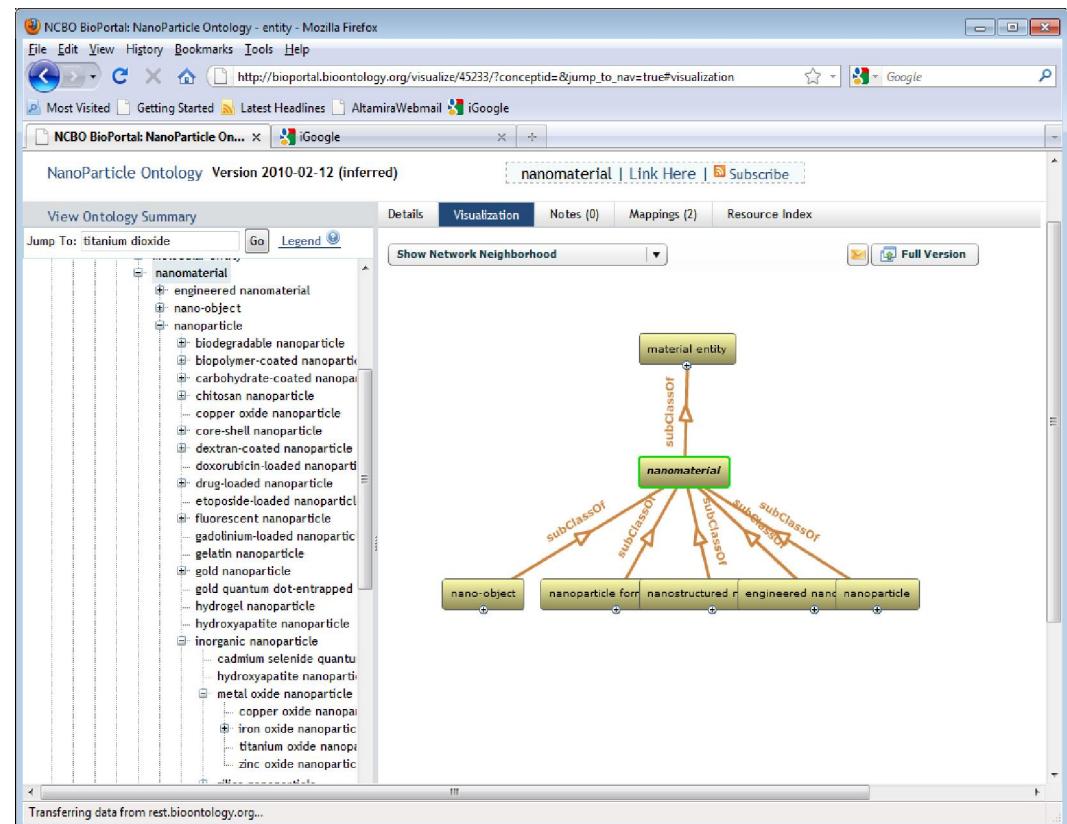
TiO₂

size 21 nm

XRD spectrum

TEM image

- + Entity
 - + object
 - + dependent
 - + independent
 - + material entity
 - + nanomaterial
 - + nanoparticle
 - + metal oxide
 - + spatial region
 - + process

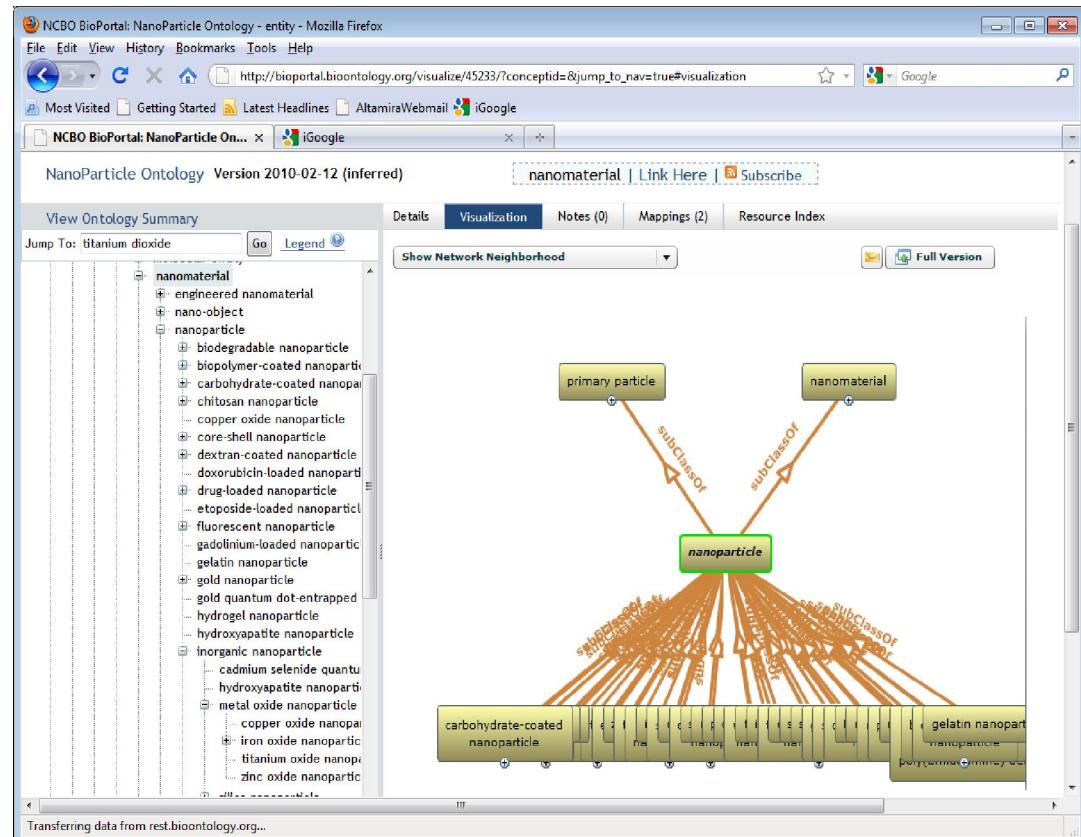


VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
AGOYDEP[CA]C[C@H]3C[C@@H](C)O[C@@H](O[C@@H]2C
(C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

Back to NPO example

TiO_2
size 21 nm
XRD spectrum
TEM image

- + Entity
 - + object
 - + dependent
 - + independent
 - + material entity
 - + nanomaterial
 - + nanoparticle
 - + metal oxide
 - + spatial region
 - + process

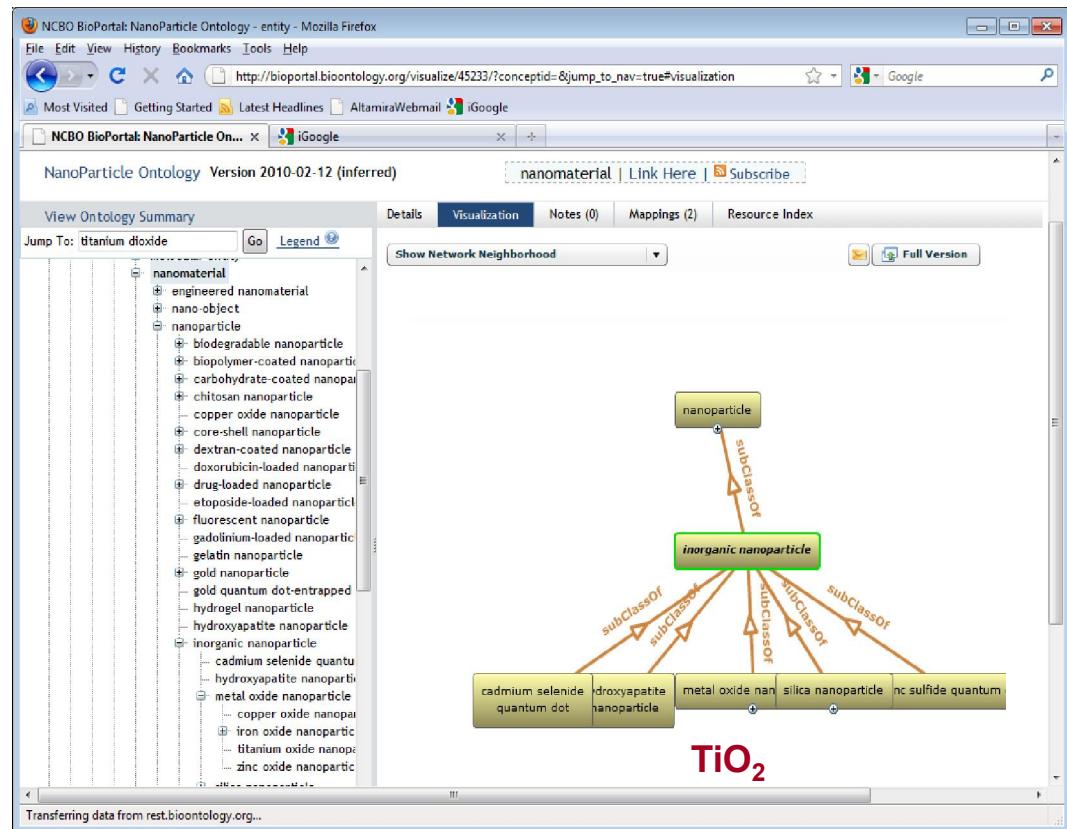


VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
AGOYDEP[CA]C[C@H]3C[C@@H](C)O[C@@H](O[C@@H]2C
(C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

Back to NPO example

TiO_2
size 21 nm
XRD spectrum
TEM image

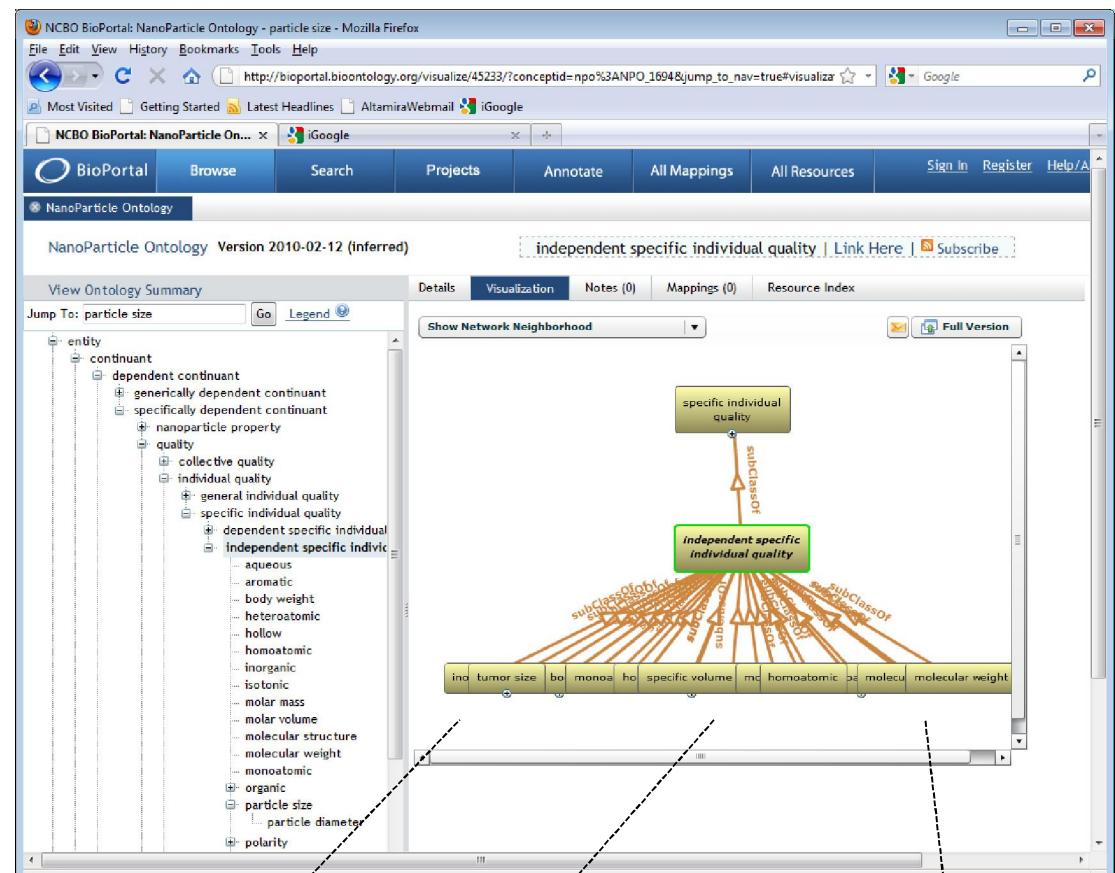
- + Entity
 - + object
 - + dependent
 - + independent
 - + material entity
 - + nanomaterial
 - + nanoparticle
 - + metal oxide
 - + spatial region
 - + process



VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
AGOYDEPGDQKPRPNSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
(C)[C@H](O[C@H]1C[C@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

TiO₂
size 21 nm
XRD spectrum
TEM image

- + Entity
 - + object
 - + dependent
 - + specifically dependent
 - + nanoparticle property
 - + quality
 - + **individual quality**
 - + molecular wt
 - + organic
 - + **particle size**
 - + tumor size
 - + spatial region
 - + process



tumor size

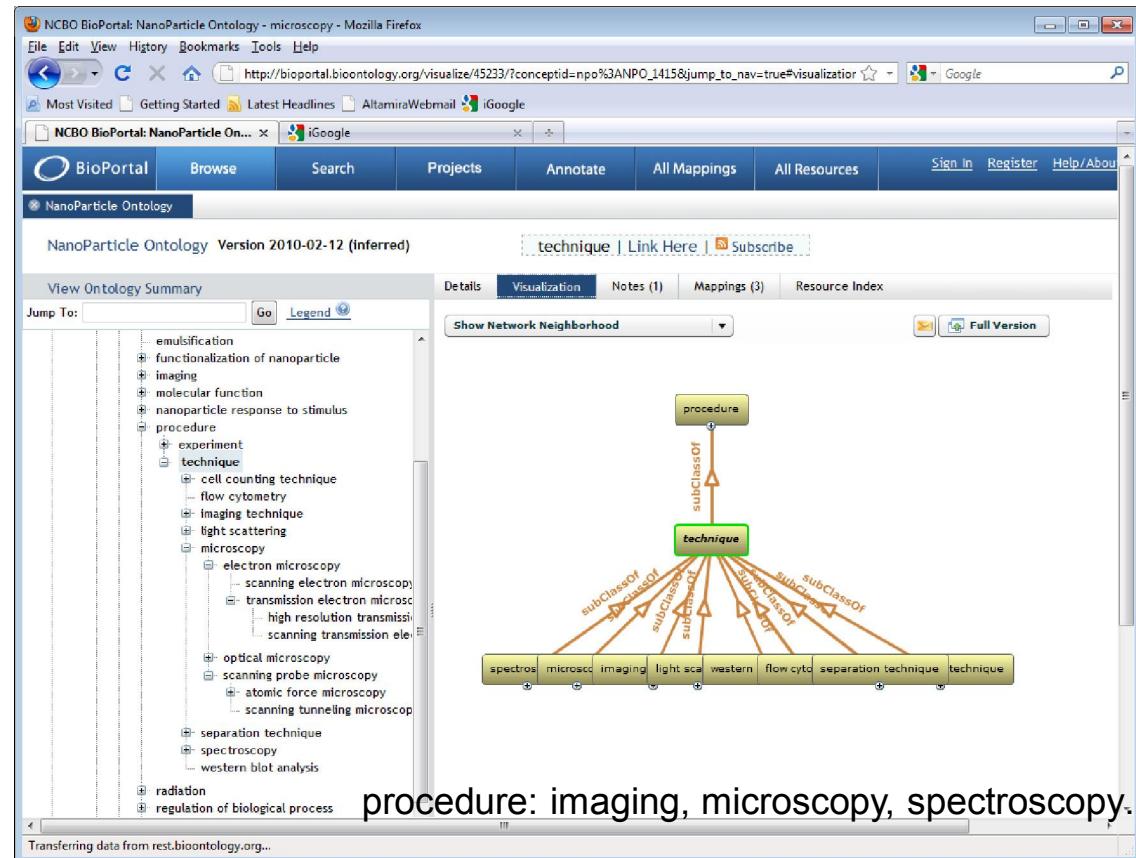
particle size

molecular wt

VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3 AGOYDEPGAKCCK-TRD-LEAID(=O)[C@@H](O)C[C@H]3C[C@@H](C)O[C@@H](O[C@@H]2C (C)[C@H](O[C@H]1C[C@@H](C)(OC)[C@@H](O)[C@H](C)O1)[C@@H](C)C(=O)O[C@H]

TiO₂
size 21 nm
XRD spectrum
TEM image

- + Entity
 - + object
 - + process
 - + process entity
 - + process
 - + biological process
 - + imaging
 - + procedure
 - + experiment
 - + technique
 - + microscopy
 - + spectroscopy
 - + spatiotemporal region
 - + temporal region



spectroscopy microscopy imaging flow cytometer

VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3 AGOYDFCAQKJERDGGEE54NCN/[C@H]3CC[C@H]([C@H]([C@H](C)[O]1)C[C@H]1(C)C(=O)O[C@H]1

ChEBI: chemical entities of biological interests

+ subatomic particles

+ role:

- + application
- + biological
- + chemical

+ chemical entity:

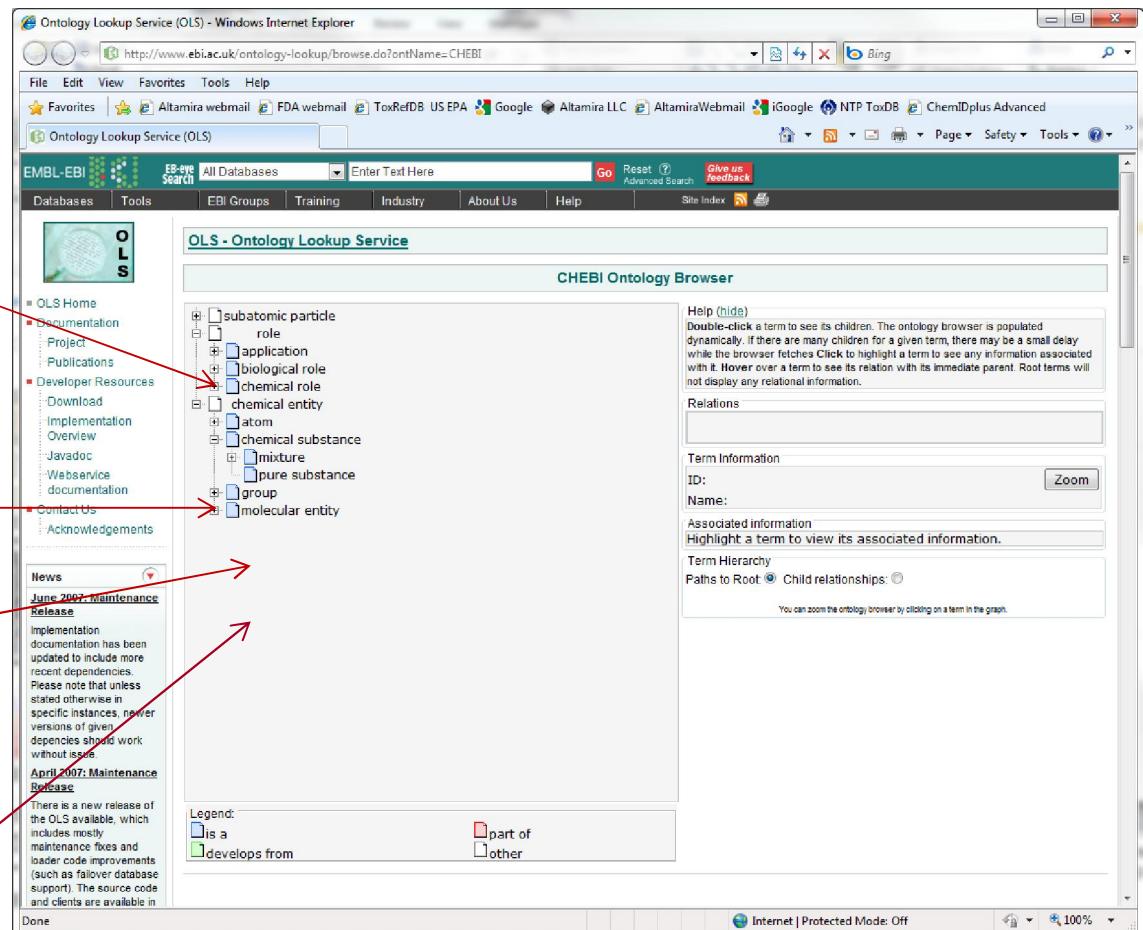
- + atom
- + chemical substance
- + group
- + molecular entity

The screenshot shows the ChEBI Ontology Browser interface. The main content area displays a hierarchical tree of chemical entities. Root terms include subatomic particle, role, application, biological role, chemical role, chemical entity, atom, chemical substance, mixture, pure substance, group, and molecular entity. A legend at the bottom defines symbols: a blue square for 'is a', a green square for 'develops from', a red square for 'part of', and a grey square for 'other'. The interface includes a search bar, navigation tabs (Databases, Tools, EBI Groups, Training, Industry, About Us, Help), and a sidebar with news and implementation details.

VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3 AGOYDEPQAOYQCL-LERDGGFESANCN(C)[C@H]3C[C@@H](C)O[C@@H](C)O[C@@H](C)O[C@@H]2C (C)[C@H](O)C@H1C[C@@H](C)(OC)[C@@H](O)C@H(C)O1)C@@H(C)C(=O)O[C@H]1

ChEBI framework – can we insert nano content?

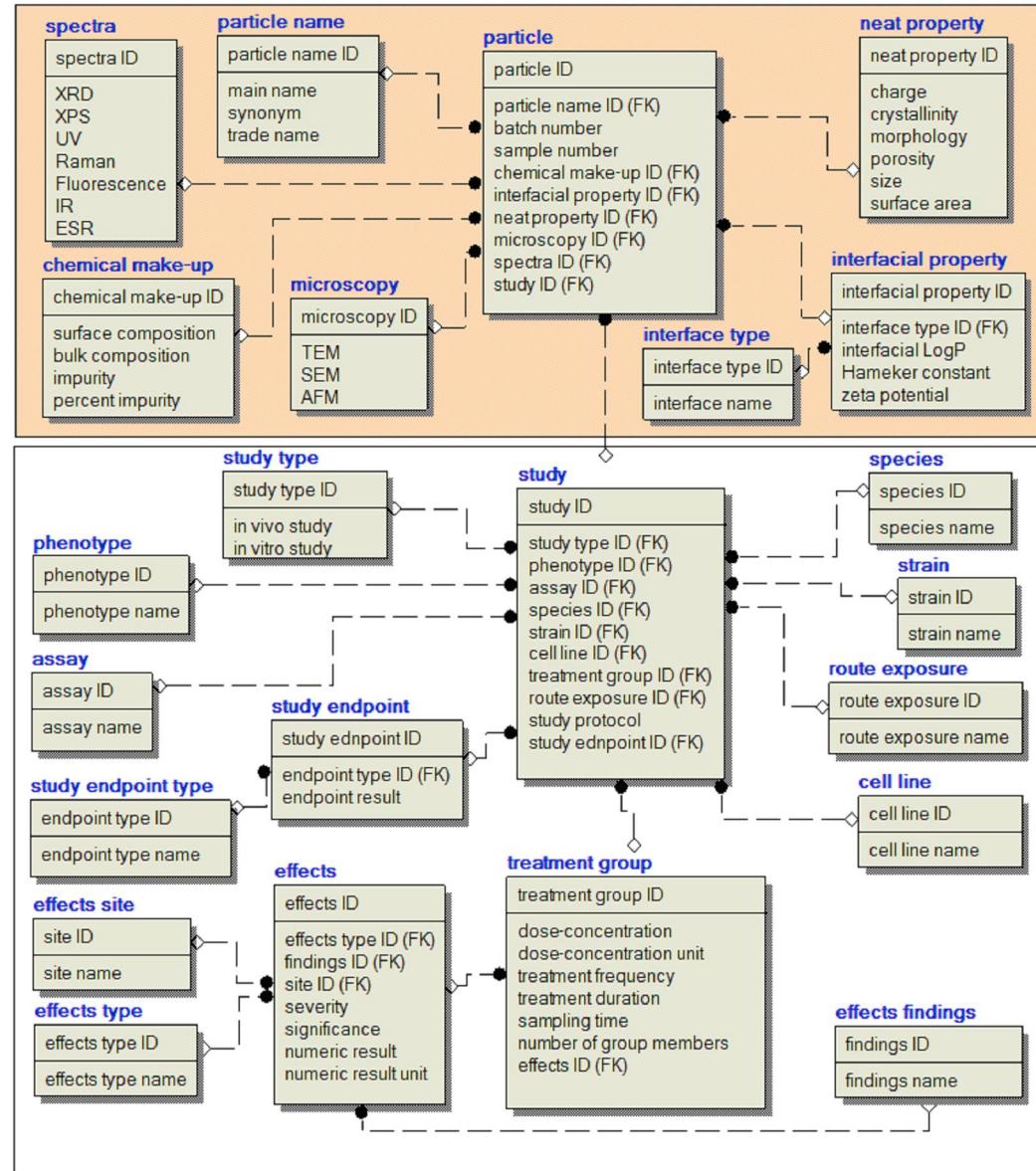
- + subatomic particle
- + role
 - + application
 - + biological role
 - + chemical role
 - + ENMparticle role
- + chemical entity
 - + atom
 - + chemical substance
 - + mixture
 - + pure
 - + ENMparticle
 - + group
 - + molecular entity
- + entity descriptions
 - + spectroscopy
 - + microscopy
 - + morphology
 - + surface
 - + chemical make-up
- + process
 - + biological process



Database – nanomaterials and toxicity endpoints

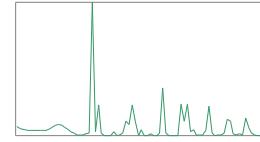
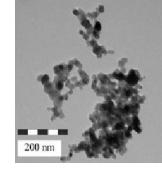
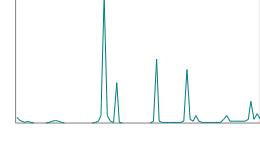
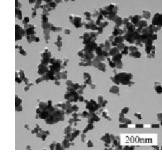
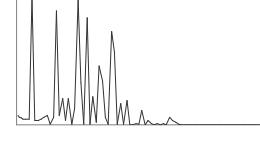
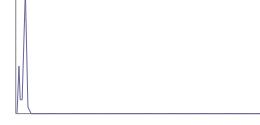
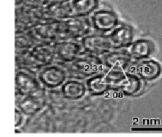
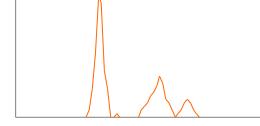
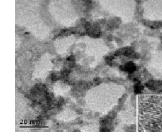
Particle Identification Characterization

In vitro and *In vivo* assays



VDUWPHTZYNWKRN-UHFFFAOYSA-NC1C3=C(C=C2C=1C(=O)C(C(=O)O)=NN2CC)OCO3
 AGOYDEP[GAD[C]L[ERD[GFT[SAN(C[C@H](C)[C@@H](C)[C@H](O)[C@@H](C)O)]C@@H](C)C(=O)O[C@H]
 (C)[C@H](O[C@H](C)[C@H](C)[C@H](C)[C@H](O)[C@@H](C)O)]C@@H)(C)C(=O)O[C@H]

Classification of nano-particles

Clusters	Particles	XRD patterns	TEM/SEM images
Metal oxides	TiO ₂		
	CeO ₂		
Zeolites	Erionite		
SWCNT	SWCNT		
Quantum dots	CdSe/ZnS		

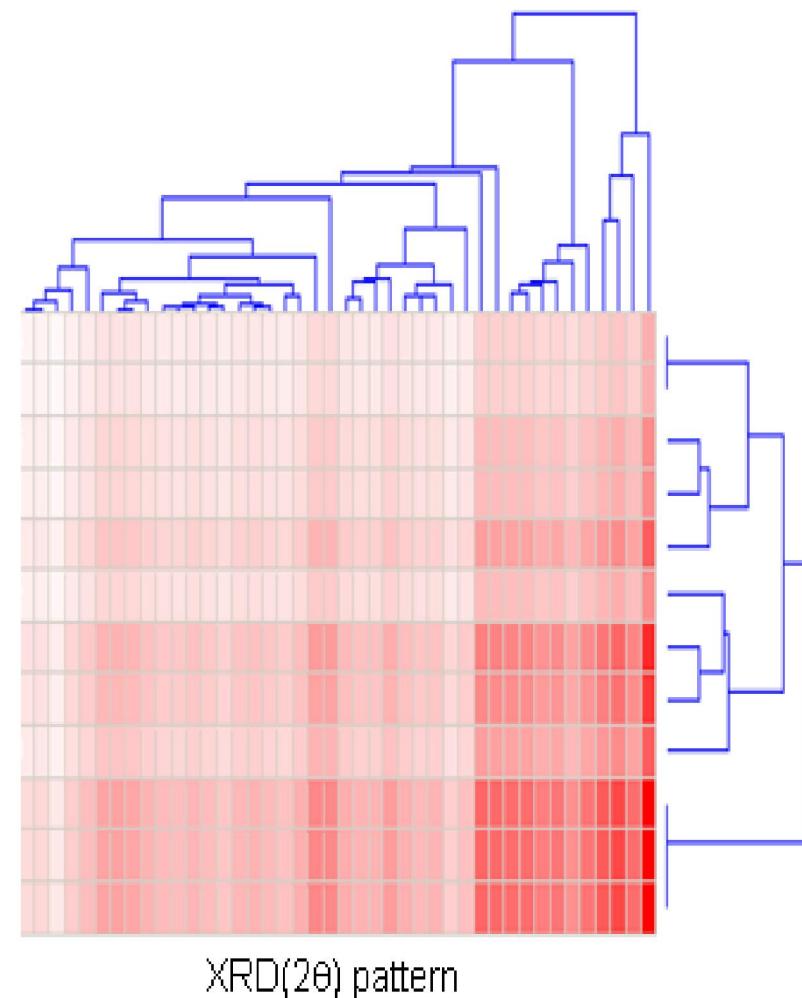
2-D clustering of 12 nanoparticles against cytotoxicity and TNF-alpha

The color intensity (the 3rd dimension) indicates activity of biological assays including inflammation (TNFalpha). This is a data mining result from a database compiled from comprehensive literature searching as of 2010 January.

Descriptors

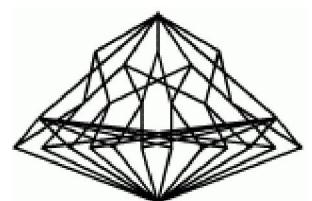
- chemical make-up
- XRD patterns
- TNF-alpha activity

Rare earth metals
Lanthanide
Transition metals G6
Other metals
Metalloids
Transition metals G2
Metals
Transition metals
Transition metals G10
Main group
Carbon
Non-metals



In summary

- We as a field need to conduct “knowledge discovery” exercises to build an ENM ontology before we start stuff things into technology (OWL or RDF).
 - Nanomaterials database based on meaningful data model is a pre-requisite to QNTR. Ontology driven data model would be highly desirable.
 - ENM Identifier
 - Minimum set of common entities for acceptable studies
 - Design of experiments (DOX, DOE)
 - Nanomaterials will force us to free ourselves from connection table driven QSAR.
 - BACK TO THE PROPERTY SPACE!



Collaborators in nano ontology and nano safety

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- Prabir Dutta, James Rathman, James Waldman - the Ohio State University (US NIFA/Nano STAR)
- Andrew Worth, JRC